REMARKS

1. Claim Amendments

New claim 74 requires use of MBL in a patient in need of, or who has already received, an organ transplant, in order to reduce a risk of an adverse condition which is associated with the organ transplantation and reducible by prophylactic or therapeutic treatment with MBL.

There is basis for prophylactic use of MBL before, during or after a "surgical or medical treatment", page 13, lines 22-24, page 10, lines 17-23.

Moreover, there is disclosure of use of MBL to treat an existing sepsis, see page 15, line 6; page 20, line 6; or other clinical symptoms associated with MBL deficiency, see page 22, lines 2-4; and of "prophylactic, ameliorating or curative treatment of a condition obtained during intensive care", see page 10, lines 28-29.

Claim 51, now dependent on 74, has been amended to require that the transplantation be an organ transplantation, and that the transplantation be associated with an increased risk of infection which might be muted by use of MBL. Claim 76 requires that the MBL be administered prior to infection (i.e. prophylactically) and 77 that it be administered in amelioration of infection.

The present invention is directed to assisting "critically ill patients", including a patient "who has sustained or is at risk of sustaining a cut life-threatening single or multiple organ failure due to disease or injury". (Page 12, lines 16-19). As a result of such failure, the patient may be in need of... transplantation...." (Page 12, lines 24-26).

It is commonplace for organ failure to be remedied by transplantation of a replacement organ. In the example, at least some patients experienced "acute renal failure requiring renal replacement therapy" (page 24, lines 14-15). The above

demonstrates that applicants were in possession of the concept of administering MBL to subjects in need of organ transplantation.

The MBL is intended for use in prophylactic, ameliorating or curative treatment of a condition arising during intensive care, see page 10, lines 28-29. The MBL can "reduce mortality from sepsis and septic shock", see page 10, line 22. "Sepsis" refers to infection, and "septic shock" to an undesirable inflammatory response to infection, such as SIRS as defined at page 11. MBL is used to "suppress states of sepsis, septic shock or multiple organ failure" (page 20, lines 15-16) "to reduce the likelihood for blood stream infections in a critically ill patient" (lines 27-28), "to reduce the likelihood of disturbance in markers of inflammations and/or inflammatory response in a critically ill patient"[1] (lines 29-31), and "to reduce the likelihood of organ replacement therapy and/or organ failure (for instance renal) in a critically ill patient" (lines 22-24). See also lines 17-19.

Claims 59-63 have been amended to clarify the oligomer/monomer terminology. The term MBL "monomer" ("subunit") is used to refer to a 96 kDa protein which itself consists of three identical 32 kDa polypeptide chains. cp. page 2, lines 15-22 of WO 00/70043 with P6, L25 of the instant application.

The MBL "oligomer" consists of a plurality of those monomers (subunits). The term "oligomer" may thus refer to a dimer, trimer, tetramer, pentamer or hexamer, consisting respectively of 2-6 such 96 kDa monomers. An MBL hexamer is 6 of the 96kDa monomers and thus 18 of the 32 kDa chains. See P6, L25-31 and page 10, lines 9-12 of WO 00/70043. WO 00/70043 is cited at P18, L26, P19, L24. See also EP 375,736 cited at P4, L8-9.

The 96 kDa monomer may thus be a molecule in its own right

---

[1] Cp. the definition of SIRS on page 11, lines 9-12.

or a component of a larger molecule.

Claims 51 and 72 have been amended to require that the "MBL" comprises one or more human MBL proteins, said human MBL proteins comprising one or more human MBL protein monomers of about 96 kDa, each monomer consisting of three human MBL polypeptide chains, each chain of about 32 kDa. It should be noted that the "mix" of monomers, dimers, trimers, etc. in the "MBL" may be different from what occurs naturally in humans. In view of the "human" limitation, claims 59 and 60 have been cancelled.

2. Unity

It is noted that the examiner's restriction between groups II and III is based on a holding of a posteriori lack of unity relative to Thiel.

In the restriction requirement of May 18, 2007, the Examiner stated: "The invention of group I was found to have no special technical feature that defined the contribution over the prior art of Thiel et al. (US Patent No. 7,202,207)".

The Examiner summarized what Thiel taught, but did not show how each limitation of claim 51 was disclosed or suggested by Thiel. The Examiner asserted merely that Thiel taught a method of preventing infection in an individual who was a) immunocompromised, b) at risk of becoming immunocompromised as a result of a "medical prevention", or c) exhibiting 50-500 ug/ml level of serum MBL.

However, the restriction did not point to any explicit teaching by Thiel of use of MBL "for the treatment of a patient suffering from systemic inflammatory response syndrome (SIRS) and/or a patient in need of transplantation and/or for reducing the risk in a patient of acquiring SIRS", per then claim 51.

In traversing the restriction, Applicants noted, "the Examiner has not made any comments re Thiel's teachings on transplantation".

The Examiner maintains the holding of a posteriori lack of unity "because independent claim 51 does not avoid the prior art of Thiel's, in addition to the art under 102 and 103 below".

We do not think it proper for the Examiner to argue, for purposes of a posteriori lack of unity, that Thiel is prior art which the claims fall to "avoid", when Thiel is not cited in any of the presently maintained prior art rejections.

We have reviewed Thiel. There is no reference to administration of MBL to individuals with SIRS, or to individuals in need of transplantation. Consequently, we do not see how the Examiner can reasonably assert that Thiel, at least in isolation, can anticipate or render obvious claim 51 and thereby create an a posteriori lack of unity.

If the Examiner believes that Thiel in combination with some other reference is patentability-destroying, then the Examiner needs to identify the combination and explain its relevance.

We note that since (1) the Examiner could have explained how Thiel anticipated or rendered obvious claim 51 in the restriction requirement but failed to do so, (2) likewise could have explained it in the instant reconsideration of the restriction but failed to do so, and (3) likewise could have applied if in this action in a prior art rejection but failed to do so, if the Examiner chooses to rely on Thiel to make a prior art rejection in the next action, that action should not be made final.

With regard to "the art under 102 and 103 below", we have explained in section 7 how claim 51, as amended, distinguishes this art.

Hence, the holding of a posteriori lack of unity must be reconsidered. Consequently, we have retained coverage of the subject matter of group III (see new claim 73).

3. Claim Objections (OA §6)

Claim 51, as examined, was directed to

> A method comprising a use of mannan-binding lectin (MBL) for the treatment of a patient suffering from systemic inflammatory response syndrome (SIRS) and/or a patient in need of transplantation and/or for reducing the risk in a patient of acquiring SIRS.

The Examiner stated, "Given the non-statutory and not appropriate for US practice (see MPEP 2173.05(q)), it is recommended that the claim recite an active, positive steps delimiting how this use is actually practiced".

Respectfully, claim 51 as presented is statutory under 35 USC §101, because it is drawn to "A method comprising a use...." The examples given in MPEP 2173.05(q) of non-statutory claims all began "The use of...."

With regard to the issue of indefiniteness, we respectfully submit that a "use of MBL" is in fact an active, positive step, albeit one whose wording might be improved.

In any event, we have amended claim 51 to recite an "administering" step, which is clearly an active step.

3B. Claim 61 has been amended to recite "and" rather than and/or, in compliance with Markush group practice. We are construing claim 61 as permitting the oligomers to be of more than one of the types recited in the Markush clause, i.e., these could be both trimers and tetramers. If the Examiner would interpret this claim differently, then 61 needs to be further amended to achieve the intended scope.

4. Definiteness Issues

4A. We have amended claim 56 to delete the term "for example", thereby making the "for example" clause mandatory.

4B. We have amended claim 61 to delete the term "preferably", thereby making the Markush group mandatory.

4C. Claim 59 has been amended to delete the first occurrence of "polypeptide monomer", there being antecedent basis

for "MBL".

4D. Claims 64-67 have been amended to recite "MBL" rather than a "medicament". Claims 68-70 have been cancelled.

5. Written Description/New Matter Rejection (OA §10)

5A. With regard to the phrase "is a mammalian polypeptide monomer" in claim 59, it was not our intent (nor a reasonable interpretation of claim 59) to read these monomers to be monomers of any mammalian protein other than MBL. MBL monomers are well known in the art; they have a molecular weight of about 96 kDa as taught in the '949 publication cited by the Examiner and acknowledged in the third paragraph of OA §13.

Basis for use of mammalian MBL polypeptide monomers may be found in original PCT claims 14, 15 and 32. However, the claims have in any event now been amended to recite human MBL proteins, human MBL protein monomers, and human MBL polypeptide chains.

5B. The Examiner also objects to the phrase "and/or" in claim 51; more precisely to the construction:

for the treatment of

a patient suffering from systemic inflammatory response syndrome (SIRS)

and/or

a patient in need of transplantation

and/or

for reducing the risk in a patient of acquiring SIRS.

Original PCT claim 1 read

> Use of a regulator of blood mannan-binding lectin (MBL) in the manufacture of a medicament to treat critically ill patients.

This is a standard European "second medical use" claim, used in EPO practice for the purposes served in the USA by method-of-

therapeutic use claims.

The anti-SIRS treatment clearly finds basis in original PCT claim 7:

> Use of a regulator of blood MBL of claim 1, in the manufacture of a medicament to treat or cure systemic inflammatory response syndrome (SIRS) in critically ill patients.

The treatment of a patient in need of transplantation clearly finds basis in original PCT claim 21:

> Use of any of the claims 1 to 16, wherein the patient is a patient in need of cardiac surgery, cerebral surgery, thoracic surgery, abdominal surgery, vascular surgery, or transplantation, or a patient suffering from neurological diseases, cerebral trauma, respiratory insufficiency, abdominal peritonitis, multiple trauma, severe burns. (emphasis added)

See also page 15, lines 31-32, and page 12, line 26.

At page 10, lines 11-23, the specification teaches

> The invention in one aspect relates to treatment of individuals admitted to ICUs, critically ill patients or to treatment of individuals who are at risk of prolonged ICU admission due to procedures/treatment known to be associated with allocations to ICUs (e.g. major surgery).
>
> Accordingly, complications arising during ICU-stay are likely to expose the individual in question to a higher risk of inflammatory conditions and indeed death. It is possible according to the invention to prophylactically treat the patients before or during procedures/treatments (e.g. major surgery) known to be associated with a risk of prolonged ICU admission. By prophylactically treating the ICU-complications before or during a treatment known to be associated with a risk of prolonged ICU admission it is possible to reduce the mortality from sepsis and septic

> shock arising during the ICU-stay.
> (emphasis added)

SIRS itself is an "inflammatory condition", which is defined at page 11, lines 9-15:

> The term "systemic inflammatory response syndrome (SIRS)", as used herein refers to the uncontrolled disease process which ensues an initial insult and which gives rise to a multi system disturbance secondary to inflammatory mediators released during shock. It can mean a response to an inflammation or injury that can be infections [sic, "infectious"] or non-infectious, defined by having two of the following: 1) Temperature above 38 degrees C or less than 36 degrees C, 2) Heat rate >90, 3) Respiration rate >20 or Paco2<32 torr, 4) WBC>12,000/mm3 or <40000, or >10% bands.
> (emphasis added)

At page 20, lines 29-31, applicants state

> Another object of present invention is to use the MBL composition to reduce the likelihood of disturbance in markers of inflammations and/or inflammatory response in a critically ill patient.
> (Emphasis added)

The term "multi-system disturbance" would clearly embrace "multiple organ failure", and at page 20, lines 15-19 applicants declare

> Another object of present invention is to use the MBL composition to suppress states of sepsis, septic shock or multiple organ failure.
>
> Another object of present invention is to use the MBL composition to reduce the risk or likelihood from [sic, "of"] multiple organ failure with a proven septic focus on post-mortem examination in a critically ill patient.

Claim 51 has been amended to recite that the MBL is administered to a patient in need of transplantation, in particular to mitigate the increased risk of infection associated with transplantation.

New claim 73 recognizes that there is an increased risk of SIRS as a result of an increased risk of infection, and hence MBL administration indirectly mitigates the increased risk of SIRs.

6. Enablement (OA §)

6.1. The Examiner first questions whether there is an adequate teaching of "how to make MBL".

The background of the invention notes that MBL is obtainable from various sources; see page 3, lines 5-21. It teaches that the general structure of MBL is shown in EP 0375573B1 (page 4, lines 8-9), and DNAs encoding MBL, or MBL peptide fragments, are discussed at page 4, line 11 to page 5, line 6. The human MBL structure is further described at page 6, line 25 to page 7, line 25. MBL production is further discussed on pp. 17-20.

Claims 51 and 74 specify that MBL comprises one or more human MBL proteins, and Applicants are not obligated to disclose the sequence of every naturally occurring form (allelic variant) of human MBL.

The Examiner notes that there are various known haplotypes of human MBL. We are not precisely sure what the point of the Examiner's discussion of MBL haplotypes might be. The invention contemplates administration of exogenous MBL. MBL sequences known to be effective in inhibiting infection are known in the art and the skilled worker would certainly be able to recombinantly produce the human MBL polypeptides characteristic of what the examiner calls the A/A haplotype. Additionally, the skilled worker could determine what mutants of MBL (e.g., conservative substitution mutants) preserve its desirable

biological activities, avoiding, for example, those point mutations which have been characterized as undesirable, (see page 1, lines 28-29).

The endogenous promoter region mutations are even less relevant in the present context than those in exon 1. That is, the skilled worker, producing human MBL recombinantly, can choose any promoter functional in the chosen host cells and is certainly not limited to use of endogenous promoters. It must be emphasized that recombinant MBL is old in the art, see e.g. page 3, lines 16-21:

> MBL can be produced in engineered cells. Recombinant MBL has been produced by mammalian cell culture (Ezekowitz, U.S. Pat. No. 5,270,1999) such as in myeloma cells, Chinese hamster ovary (CHO) cells, human hepatocytes, and human embryonic kidney (HEK) cells (Vorup-Jensen,-T et al. Int Immunopharmacol. 2001 Apr; 1(4):677-87) or by expression of MBL in methylotrophic yeast strains as for instance described in US6337193.

The relevance of the haplotype discussion is thus limited to the use of plasma-derived MBL, see page 3, lines 23-26. However, the skilled worker would naturally pool plasma from subjects of acceptable haplotypes. It should be noted that the subjects with "low MBL" promoter haplotypes produce a perfectly functional MBL, they just don't produce as much of it as someone whose MBL promoter region is normal. And if a subject is producing an allelic variant of MBL, its acceptability for inclusion in pooled plasma-derived MBL would depend on its activity, which can be ascertained without undue experimentation.

6.2. The Examiner questions whether there is sufficient description of how to transplant "any organ" using the claimed MBL. It should be understood that the MBL is not administered to reduce the risk of rejection of the transplant. Rather, its

principal purpose is to reduce the risk of subsequent infection.

Organ transplantation is a mature technology, and it should not be necessary to make specific disclosure of transplantation techniques. Such are descried in various textbooks, such as Ginns, et al., Organ Transplantation (1999).

Statistics on the incidence of transplantation in the USA, 1996-2005, in transplants per million population, are given at www.ustransplant.org/annual_reports/current/default.htm, and reproduced below

	Year of Transplant									
	1996	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**
Liver	15.39	15.63	16.71	17.42	17.70	18.19	18.49	19.50	21.00	21.73
kidney	42.97	43.70	46.07	46.79	48.23	50.00	51.25	52.05	54.51	55.59
pancreas	0.20	0.30	0.33	0.51	0.47	0.59	0.62	0.54	0.62	0.66
Pancreas after kidney	0.43	0.49	0.58	0.81	1.08	1.07	1.30	1.18	1.43	1.16
Kidney pancreas	3.25	3.19	3.60	3.45	3.24	3.12	3.14	3.00	3.00	3.05
Intestine	0.17	0.25	0.26	0.27	0.29	0.39	0.37	0.40	0.52	0.59
Heart	8.83	8.56	8.69	8.02	7.79	7.72	7.47	7.07	6.87	7.17
Lung	3.07	3.48	3.22	3.27	3.40	3.71	3.61	3.73	3.99	4.75
Heart-lung	0.15	0.23	0.17	0.19	0.17	0.09	0.11	0.10	0.13	0.11

6.3. The Examiner asserts that the role of MBL in transplantation is contradictory.

> In order for this therapy to be predictable, the MBL must play a role in transplantation. However, Hjelmesaeth et al (J Am Soc Nephrol 17:1746-1754, 2006) teach that serum levels of MBL was not significantly associated with patient survival, cardiovascular (CV) death, or graft loss (see abstract). Further,

> Hjelmesaeth et al teach that MBL was not associated with 8-yr survival or CV death. This finding is supported to some extent by Dahl et al (J. Exp. Med. 199:1391-1399, 2004) results of a large Danish population-based follow-up study (8-24 yr) of approximately 10,000 adults that showed that MBL deficiency is not a major risk factor for morbidity and death. Dahl et al found that no evidence for differences in infectious disease or mortality in MBL-deficient individuals versus controls. Dahl et al conclude that their result suggest that MBL deficiency is not a major risk factor for infection, other serious common diseases, or death in the adult Caucasian population (see page 1397, last ¶). Further, support come from Berger et al (Am J Transplant 5: 1361-1366, 2005) who teach that higher MBL levels seem to be associated with a more severe from of rejection leading to treatment failure and graft loss (see abstract). Berger et al (J Am Soc Nephrol. 2007 Aug; 18(8):2416-22) teach that Low pretransplantation mannose-binding lectin levels predict superior patient and graft survival after simultaneous pancreas-kidney transplantation (see title). Furthermore, US 2004/0259771 teaches and claims methods of treating transplantation using MBL inhibitors (see published claims 40 and 44).

Hjelmesaeth et al. looked at the correlation between MBL in early post-transplantation (first 10 weeks) with long-term patient survival, graft survival, and cardiovascular death in renal transplant recipients without diabetes. They reported that there was no association. However, it does not appear that they looked at the incidence of infection in these transplant recipients.

The Dahl (2004) study is alluded to by Hjelmesaeth on page 1750 col. 2 (ref [46]). The Dahl study looked at the association between MBL deficiency (MBL alleles B, C and D) and the risk of infection, morbidity leading to hospitalization, and death, in

the Danish adult general population (not transplant recipients). However, the Examiner fails to mention that Dahl states

> MBL deficiency may only come into play when other parts of the immune system are compromised, e.g. by chemotherapy....MBL deficiency has been associated with increased risk for severe and recurrent infections, but almost solely in hospital studies.

The instant invention relates to management of critically ill patients for whom "hospital studies" would be relevant.

The Examiner also fails to acknowledge Hjelmesaeth's statement that his "results are in contrast with the Japanese 3-yr follow-up study of hemodialysis patients that showed lower serum MBL concentrations in nonsurvivors" (page 1750, col. 2).

The Examiner relies on Berger (2005) for the proposition that higher MBL levels (>400 mg/ml) are associated with a more severe form of rejection of kidney transplants, leading to treatment failure and graft loss[2]. Higher MBL levels were attributable to endogenous factors, rather than to administration, so we don't know whether the same rejection pattern would be seen in MBL-deficient individuals receiving MBL replacement therapy. Berger (2005) at page 1365, suggests mechanisms whereby MBL might influence the outcome of a kidney transplant.

Berger (2007) made similar findings in diabetic patients simultaneously receiving pancreas and kidney transplants, that is kidney and pancreas graft survival and patient survival levels were lower in subjects with MBL >400 ng/ml. Possible mechanisms are discussed on page 2419.

It is interesting to note that Berger (2007) acknowledges "a recent study failed to show an association between MBL levels

---

[2] But the association with patient survival was not significant (Fig. 3 and page 1363 col. 2).

and patient or graft survival after kidney transplantation". That study was the Hjelmesaeth (2006) paper discussed above.

It therefore does not appear that the Examiner has conclusively demonstrated that MBL would have an adverse effect on graft or patient survival after renal (or pancreatic) transplantation. Even if it did, it might still provide net benefits for some transplant patients, e.g., liver transplant patients.

Regardless of what effect MBL might have on acceptance of the graft, the MBL is still useful post-transplantation, in inhibiting infection.

Applicants present two declarations under 37 CFR 1.132 from an expert, Dr. Alison Freifeld. The 5 page declaration may be considered as "I", and the 2 page one as "II", for convenience.

In support of the claimed efficacy of MBL in a transplantation context, Freifeld Declaration I presents preliminary results from an ongoing liver transplant study. The pharmacodynamic response of MBL administration is measured as the rise in C4 complement concentration. These data show that administration of rhMBL normalizes complement C4b deposition (a marker for activation of the MBLectin complement pathway) and that C4b deposition correlates with rhMBL levels.

6.4. The Examiner also finds that the specification does not provide sufficient guidance for one skilled in the art to use MBL to transplantation to the extent that the MBL level in the patient is kept between 1000-2000 ng/ml. The prior art describes methods for administration of MBL and methods for determining MBL serum levels. The person skilled in the art, based on the prior art, would know how to measure and keep the MBL level in the patient between 1000-2000 ng/ml. This is for example described in WO 00/69894 and US 6,562,784. These references cite that the MBL level is measured in serum or plasma, and may be determined by time resolved immunofluorescent assay (TRIFMA) or ELISA. A

suitable TRIFMA assay for determining MBL levels in serum is described in detail in WO 00/69894 on p. 11, l. 10-18 and in US 6,562,784 in paragraph 6, lines 18-30.

7. Prior Art Issues

7.1. Per OA §13, claims 51-52, 54-67 and 71-72 stand rejected as anticipated under 102(e) by O'Brien, US2005 0037949A1 ('949).

The instant application is the U.S. national stage of PCT/BE03/00158, filed September 23, 2003. That date is after November 29, 2000, so new 102(e) applies.

The '949 application was domestically published under 35 USC 122(b) and hence, under 35 USC 102(e)(1), its reference date is its US filing date. Since it was an international application designating the US, it is treated as though its US filing date was its international filing date of April 24, 2003.

While it has Australian priorities of April 24 and December 13, 2002, those are irrelevant for purposes of 102(e). See MPEP 2136.03.

35 USC 102(e) compares the reference date to applicant's date of invention. Applicant may rely on foreign priorities if the priority application supports the claim.

Applicant has asserted a British priority of September 23, 2002, which is earlier than the 102(e) effective reference date of O'Brien '949[3]. Hence, the rejection must fail.

7.2. It is noted that the rejection beginning on page 15

[3] This foreign priority is clearly listed on the front page of applicant's PCT publication (WO2004/026330) and is re-asserted in the ADS filed March 23, 2005. The International Bureau acknowledged receipt of the priority document (Ex. A) and the IB should have transmitted copies to the designated offices. Consistent with this expectation, the Notification of Insufficient Fees mailed December 7, 2005 acknowledged "priority documents filed on 03/23/2005". Hence, applicants may rely on their foreign priority.

and the rejection beginning on page 16 are both identified as section 15.

7.3. At page 15, claims 51 and 68-70 are rejected as obvious over the '949 publication in view of Seilhammer, USP 6,245,334.

This rejection fails because the primary reference has too late a date of publication (February 17, 2005 domestic, and November 6, 2003 in PCT) to be prior art under 102(a) or (b), and too late a filing date to be prior art under 102(e), given applicant's September 23, 2003 international filing date and September 23, 2002 British priority date..

7.4. At page 16, claims 51 and 68-70 are rejected as obvious over the '949 publication in view of Mullighan (2002).

Mullighan apparently observed that MBL coding and promoter polymorphisms were associated with an increased risk of infection following allogeneic stem cell transplantation (SCT).

Mulligan suggests that "if MBL deficiency is confirmed by future genetic and functional studies to be a major risk factor for infection after SCT, this clinical setting would be an ideal scenario for a clinical trial of MBL replacement therapy".

Claim 51 has been amended to specify organ transplantation. Transplantation of organs is distinctly different from transplantation of stem cells, as explained in the attached Freifeld Declaration II.

In particular, the incidence of post-operative infections is much higher after organ transplantation than after stem cell transplantation. Since one purpose of the administration of MBL is to mitigate this risk, this distinction is highly relevant to patentability.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By:_____
Iver P. Cooper
Reg. No. 28,005

Enclosures
-Freifeld Declarations I (5 pp.) and II (2 pp.)
-Ex. A (IB acknowledgment of priority documents)
-Platt (2002)
-Bouwman et al. (2005)
-Dunn & Acton, Chap. 3, "Solid Organ Transplantation"

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
G:\ipc\g-i\hoib\BERGHE1\pto amend.wpd